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CLINICAL THERAPEUTICS

Successful Treatment of *Saksenaea* sp. Osteomyelitis by Conservative Surgery and Intradiaphyseal Incorporation of Amphotericin B Cement Beads

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ABSTRACT Osteoarticular mucormycosis cases are quite rare and challenging infections that are mostly due to direct inoculation during traumatic injury among immunocompetent patients. Classic management includes a combination of aggressive surgical debridement, which may lead to amputation, and long-term systemic liposomal amphotericin B therapy. This article describes the successful treatment of *Saksenaea* sp. osteomyelitis in a patient with diabetes mellitus, using a combination of systemic antifungal therapy and conservative surgery with insertion of amphotericin-impregnated cement beads.

KEYWORDS *Mucorales*, amphotericin B, antifungal agents, osteomyelitis

Mucorales osteomyelitis still presents diagnostic and therapeutic challenges and is associated with high mortality rates despite a combined therapeutic strategy involving antifungal treatment and surgery (1). Members of the order *Mucorales* are present in soil and plant debris and could be responsible for osteoarticular mucormycosis as a consequence of contamination through disrupted cutaneous barriers after traumatic injury (2). Surgical management is classically aggressive and complicated, with poor functional outcomes or even amputation. We report the first successful conservative orthopedic treatment of *Saksenaea* sp. osteomyelitis in a patient with diabetes mellitus, using *in situ* amphotericin-impregnated cement beads in combination with systemic posaconazole therapy.

A 63-year-old man was admitted for a painful and swollen right ankle. He had well-controlled diabetes mellitus, hypertension, and degenerative arthritis. He lived in France and had never travelled overseas. Seven years earlier, he had suffered ankle trauma due to a rockfall and developed a necrotic subcutaneous abscess and a diaphyseal periosteal reaction seen on X-ray films. He underwent surgical drainage of the abscess; the sample cultures remained sterile and the surgical wound outcome was marked by a purple painless cutaneous infiltration. Seven years after the first operation, the patient's ankle became painful again and a bone biopsy was performed, which revealed no microorganisms in cultures. Empirical broad-spectrum antibiotherapy was initiated, without efficacy. Lower leg pain, erythema, and edema worsened and a satellite, 4-cm, right inguinal area of lymphadenopathy appeared. The patient was afebrile and had moderate biological inflammatory syndrome (C-reactive protein level, 50 mg/liter). Magnetic resonance imaging (MRI) showed decreased signal intensity on

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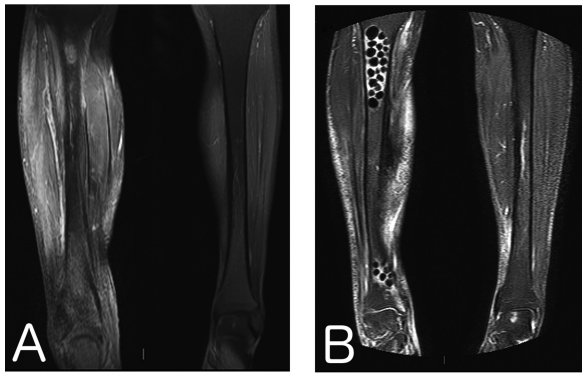

FIG 1 MRI images. (A) Initial MRI (coronal section; T2-weighted sequences). Abnormal bone marrow signaling increased after injection (osteitis) from the right tibia. Major edema and subcutaneous contrast uptake are evident. (B) MRI performed 3 months after surgery (coronal section; T2-weighted short-tau inversion recovery [STIR] sequences). Regression of abnormal bone and subcutaneous signals is evident, with visualization of the amphotericin B-impregnated cement beads.

T1-weighted images and increased signal intensity on T2-weighted images of the superior tibial metaphysis, fibular diaphysis, and calcaneum, with pathological signals of subcutaneous and musculotendinous structure extension but without evidence of abscess or arthritis (Fig. 1A).

Six months later, bone, skin, and muscle biopsies were repeated. Histopathological examination revealed an inflammatory granuloma and a nonspecific inflammatory infiltrate. Grocott staining revealed nonseptate large hyphae, without signs of angioinvasion, and cultures grew a methicillin-susceptible *Staphylococcus aureus* strain and a filamentous fungus. The fungal isolate was sent to the French National Reference Center for Invasive Mycoses and Antifungals and was identified as *Saksenaea* sp. Microscopic examination of the expanding white-grayish colonies showed unbranched conidiophores, dark rhizoids, and the distinctive flask-shaped multispored sporangia that represent a key attribute of the genus (3, 4). A multilocus sequencing analysis did not allow assignment to the species level, due to the absence of significant sequence similarity in public databases. Antifungal treatment with intravenous liposomal amphotericin B, at up to 7.5 mg/kg/day, was initiated. Additionally, the bacterial coinfection was treated with clindamycin and fusidic acid for 3 months. One month after the initiation of antimicrobial therapy, local inflammation decreased and MRI showed stable lesions. Liposomal amphotericin B treatment resulted in renal failure, leading to a switch to posaconazole treatment (400 mg twice a day). Due to the partial response to medical treatment, intolerance to the standard treatment, and the persistence of large bone lesions, surgery was performed, with abscess debridement and insertion of cement beads impregnated with amphotericin into the three infected sites, i.e., tibial proximal extremity, tibial diaphysis, and fibula (Fig. 2A). Surgical samples were necrotic (Fig. 2B), and cultures were still positive for *Saksenaea* sp. Serum and bone marrow posaconazole levels were 0.55 mg/liter and 0.72 mg/liter, respectively, indicating good local penetration. Oral posaconazole treatment, with optimal plasma concentrations, was pursued for 6 months. One month after surgery, wound healing was complete and subcutaneous swelling and pain had significantly improved. MRI evaluation performed 3 months after surgery showed regression of abnormal signals for bone and muscle (Fig. 1B). Unfortunately, the patient developed aggressive metastatic rectal carcinoma in the same year and died 6 months later, despite surgical and chemotherapeutic treatment.

Saksenaea is a genetically heterogeneous mucoralean genus that is strongly associated with soil and is distributed worldwide. The genus currently includes four species, *Saksenaea vasiformis*, *Saksenaea erythrospora*, *Saksenaea oblongispora*, and *Saksenaea loutrophoriformis* (4–6), all isolated from clinical samples. The phylogenetic analysis, which was based on the DNA sequences of three genes (internal transcribed spacer [ITS], large subunit [LSU], and translation elongation factor 1-alpha [TEF1-α] genes) from the patient's strain,

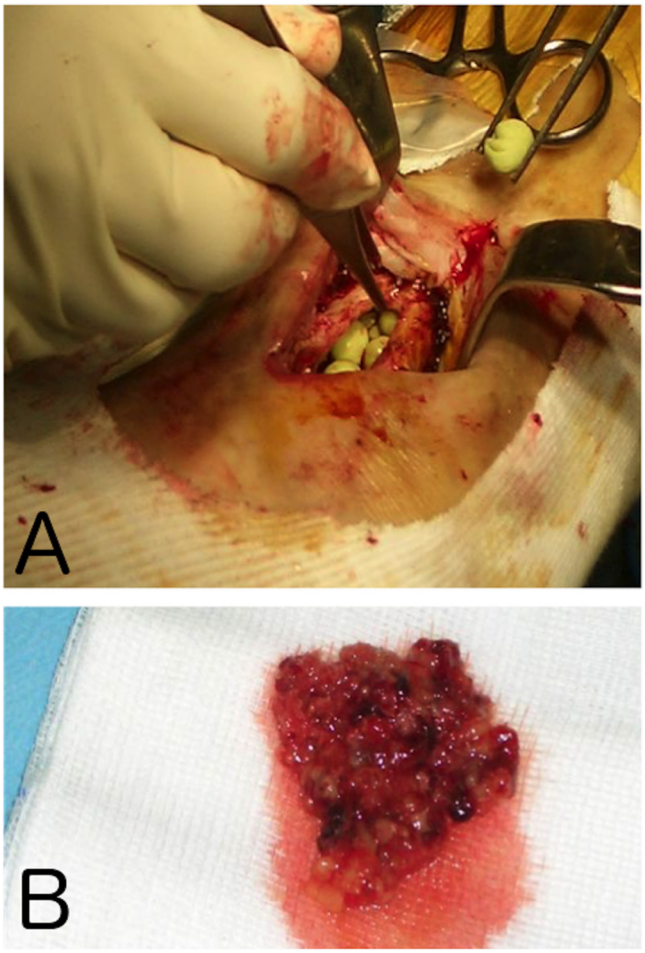

FIG 2 Intraoperative photographs. (A) Extensive debridement with enlarged cortical window and placement of cement beads impregnated with amphotericin B. (B) Bone marrow necrosis.

suggested evidence of the existence of a cryptic species in the genus *Saksenaea*. Human infections caused by *Saksenaea* species represent only 2% of reported mucormycosis cases and 9% of posttraumatic mucormycosis cases, behind other species such as *Absidia*, *Apophysomyces*, *Rhizopus*, and *Mucor* species (2, 7–9). However, this apparent low incidence may be partly explained by culture failure in routine mycological media, as this fungus needs nutritionally deficient medium or Czapek-Dox agar medium to sporulate (9). Most *Saksenaea* infections are observed in tropical and subtropical areas (8), with the spectrum of clinical presentations being closely related to the patients' immunological status. Infections are mostly subacute or chronic cutaneous infections secondary to traumatic inoculation of contaminated soil and affect immunocompetent patients. In immunocompromised patients, other described manifestations of *Saksenaea* sp. infections are rhinocerebral involvement and disseminated infections (10).

Osteoarticular mucormycosis cases are quite rare and challenging infections. Only 34 osteoarticular infections due to mucormycetes were reported in a recent review (1), including only 1 patient with a bone infection due to a member of the *Saksenaea* genus (*S. vasiformis*). The patient underwent a leg amputation to obtain a recovery, due to persistent drainage despite multiple debridements and amphotericin B treatment (11). That review reported a mortality rate of 24% for patients with osteoarticular mucormycosis. However, accurate early diagnosis and long-course therapy with a combined medical-surgical approach may result in favorable outcomes (1). Recent guidelines proposed a multimodal approach for management of posttraumatic *Mucorales* bone and joint infections, including surgical debridement (to clear margins) (12) and long-term antifungal treatment using

high-dose liposomal amphotericin B. Surgical management could be aggressive, leading to amputation when clinical improvement is not obtained despite adapted antifungal treatment or when the treatment leads to severe toxicity.

Here we report the first successful conservative orthopedic treatment of *Saksenaea* sp. osteomyelitis, using *in situ* amphotericin treatment in combination with systemic posaconazole therapy. This azole agent was reported to exhibit good *in vitro* activity against *Saksenaea* sp. strains and was successfully tested in a murine model of disseminated infection (13, 14). Furthermore, posaconazole is recommended as salvage therapy for mucormycosis among patients who have refractory infections or are intolerant to prior antifungal treatment (12–15). In addition to systemic treatment, intradiaphyseal amphotericin B-impregnated cement beads yielded high and prolonged locally effective concentrations of antifungal agent without systemic toxicity. The success of amphotericin B-impregnated cement has already been reported for the treatment of *Mucorales* osteomyelitis and soft tissue infections (16–18), and this strategy deserves to be considered, in combination with optimal systemic treatment; it could result in conservative treatment of these infections, which are usually associated with poor functional prognoses.

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